The Double Trouble: PVD and Peripheral Neuropathy in Diabetes

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Diabetes, one of the largest global health emergencies of the 21st century, affects humankind irrespective of the socioeconomic status and geographical location. The recent worldwide statistics indicate that one out of every 11 adults has diabetes with one death occurring every six seconds. India, having more than 69 million people with diabetes, is the largest contributor to regional mortality, accounting for 1 million deaths attributable to diabetes. An increase in the prevalence of diabetes increases the complications of the lower extremities, viz., Diabetic Peripheral Neuropathy (DPN), Peripheral Vascular Disease (PVD) and Diabetic Foot Ulceration (DFU), which are twice as prevalent in diabetics as compared to non-diabetics.

Diabetic foot disease has major consequences in terms of morbidity and associated mortality. It is estimated by many longitudinal epidemiological studies that the risk of development of foot ulcer is about 25% among persons with diabetes during their lifetime. Perhaps, the most worrisome aspect is that, almost 85% of the amputations are preceded by DFUs. A DFU is defined as a full thickness lesion of the skin distal to the malleoli in a person with diabetes mellitus. Amongst its multiple contributing causes, DPN and PVD are the main etiological factors. Others causative factors include unrecognized trauma, biomechanical abnormalities, limited joint mobility and increased susceptibility to infections.

Nerve damage in diabetes affects the motor, sensory, and autonomic fibers. Muscle weakness, atrophy and paresis are caused by motor neuropathy while sensory neuropathy results in loss of the protective sensation of pain, pressure and heat. This loss of sensation, particularly in the feet, leads to repetitive minor injuries from internal (calluses, nails, foot deformities) or external causes (shoes, burns) that go unnoticed at the time. Foot deformities such as prominent metatarsal heads, clawed toes and Charcot neuroarthropathy are strongly associated with and predictive of increased plantar pressure and foot ulceration. DPN, apart from increasing the risk of ulceration, also inhibits the healing by increasing forces on certain parts of the foot while walking (as a result of motor neuropathy) and by a loss of protective behavior (as a result of sensory neuropathy).

PVD is defined as any atherosclerotic arterial occlusive disease below the level of the inguinal ligament, resulting in a reduction in blood flow to the lower extremities. PVD, an important risk factor for impaired wound healing and lower extremity amputation, is 2-8 times more prevalent in diabetics, starts at an earlier age, develops more rapidly and is more severe as compared to non-diabetics. It is also associated with atherothrombosis of other vascular beds, including the cardiovascular and cerebrovascular systems. At the same time, identifying PVD in patients with DFUs is important because its presence is associated with worse outcomes, such as a slower (or lack of) healing of foot ulcers, higher risk of developing ischemic ulcers, gangrene and lower extremity amputations, subsequent cardiovascular events and premature mortality. PVD related studies predict a positive trend between PVD severity and amputation in diabetics. People with diabetes are 15 times more likely to have an amputation than those without. Even minor injuries accompanied by infection increase the demand for blood in the foot and an insufficient blood supply results in DFU, leading to limb amputation. PVD also inhibits healing by disrupting the processes needed for re-epithelialization. Thus, both PVD and DPN not only predispose a diabetic to the development of ulcers but also to slow healing.

Understanding the classification of DFUs is essential in order to establish an appropriate treatment plan and follow up. Experts have proposed various classifications for DFUs. Most of these take into account the size and depth of the ulcer, presence or absence of gangrene, neuropathy or arterial insufficiency. Several DFU classifications only include the presence or absence of infection.
Forrest’s, Knighton’s, the Texas Diabetic Wound Classification and the Ten-Level Seattle Wound are the best known classification systems for DFUs. DFUs, based on the presence or absence of ischemia, are categorized as neuropathic, ischemic and neuro-ischemic. In Neuropathic Ulcer (NPU), neuropathy dominates in the absence of ischemia. In ischemic ulcer (IU), PVD is predominant devoid of neuropathy, while in Neuro-ischemic Ulcer (NIU), PVD and neuropathy co-exist. NPUIs frequently occur on the plantar surface of the foot, or in areas overlying a bony deformity. IUs and NIUs are more common on the tips of the toes or the lateral borders of the foot. NIUs result in the worst outcomes, which include poor healing, longer healing times, higher ulcer recurrence, greater risk of amputations and higher mortality. NIUs have risen since the 1990s (from 1/3 to over 1/2 of all foot ulcers), thereby becoming the most common etiology of DFUs.

Distinguishing between these entities is mandatory for inter-clinician communication, assessment of healing tendency and determination of treatment options. India-centric data pertaining to the prevalence, risk factors and co-existence of DFU etiologies is scarce, due to a lack of outpatient and clinic-based surveillance systems. In this context, a study by Bajaj S, et al titled “Peripheral Vascular Disease in patients with Diabetic Foot Ulcers- An emerging trend: A prospective study from North India” has tried to shed light on the prevalence of PVD in DFUs as well as compare the clinical profile and risk factors responsible for development of NPU and NIU in a North Indian population. 100 type 2 diabetes mellitus (T2DM) patients (approximately 10% of the 1,244 T2DM patients who visited the outpatient department) presenting with foot ulcers in a tertiary referral Centre at Jalandhar were evaluated.

The authors reported a DFU prevalence of 8.02% in the population studied. This prevalence is approximately twice that reported in different nations like Kenya (4.6%) and The United States (4.1%). The 30% prevalence of NIU reported in this study is in accordance with other studies reporting an occurrence ranging from 23.3% - 30.5%.

All the risk factors evaluated viz. gender, duration of diabetes, smoking habits, hypertension, coronary artery disease (CAD), stroke, nephropathy and retinopathy, were found to be highly associated with NIU than NPU. NIU was more prevalent among males (32.8%) as compared to females (25%). Smoking, the most important contributory risk factor responsible for male predominance, was strongly correlated with NIU (67%) than NPU (17%) (p<0.0001). Smoking leads to vascular wall thickening, reduction in blood circulation and ischemic changes in the affected neurons, resulting in loss of sensation and increased predisposition to injuries. Hypertension was the second most important risk factor for NIU with 80% NIU patients being hypertensive.

Poor glycemic control was found to be a risk factor for both NIU (HbA1c 10.1%) and NPU (HbA1c 9.6%) while the average duration of diabetes was found to be longer in patients with NIU than with NPU (14 years vs 8 years) (p=.015). The present study also found that the patients having NIU had higher prevalence of other complications of diabetes as against patients having NPU, such as retinopathy (80% vs 50%, p=0.007), nephropathy (50% vs 34%, p=0.18) & CAD (27% vs 13%, p=0.14). The significant relationship between retinopathy and DFU reflects a widespread microangiopathy. Taken together, smoking, hypertension, retinopathy and the duration of diabetes were significantly associated with the risk of NIU while the other risk factors like CAD, stroke, nephropathy and the male gender were non-significantly associated with NIU.

The authors opine that the higher incidence of NIU (30%) reported in this study vis-à-vis that reported earlier from South India (5%) could be due to increasing age of the diabetic population, consequent increase in the duration of diabetes from the time of diagnosis, increase in the incidence of smoking and the prevalence of uncontrolled hypertension. Considering the underestimation of NIU in clinical practice, the study recommends examination of peripheral pulses in all diabetic patients and ankle brachial index in DFU patients.

The authors of this study have called for a multidisciplinary approach in DFU patients by providing foot care education, targeting early detection, managing controllable risk factors and aggressive treatment of NIU. The information provided by this country specific study is a valuable addition to our understanding of the current etiology of DFUs in India. With the alarming increase in the prevalence of diabetes and a subsequent increase in the incidence of DFUs, prevention and proper management of diabetic foot takes Centre stage. Reducing amputations, preserving the quality of life and improving survival among patients with diabetes will help reduce the burden of this complex, costly and disabling complication of diabetes.

References

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